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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte AVI TOVI, CHAIM EIDELMAN, SHIMON SHUSHAN, ALON HAGI, ALEXANDER IVCHENKO, GABRIEL-MARCUS BUTILCA, LEAH BAR-OZ, TEHILA GADI, and GIL ZAOVI

Appeal 2016-002044
Application 13/850,096[1]
Technology Center 1600

Before ERIC B. GRIMES, FRANCISCO C. PRATS, and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134(a) involves claims to a method of preparing Bivalirudin, an anticoagulant peptide. The Examiner rejected the claims as lacking adequate descriptive support in the Specification, and also for obviousness.

We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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[1] Appellants identify the real party in interest as Teva Pharmaceuticals USA, Inc. App. Br. 2.

STATEMENT OF THE CASE

Bivalirudin, also known as "Hirulog-8" and "Angiomax®," is a potent thrombin inhibitor and anticoagulant. Spec. ¶¶ 3–5. Bivalirudin is a peptide composed of 20 amino acids. *Id.* ¶ 4.

Appellants' invention is a method of producing Bivalirudin "based on a solid phase synthesis or a combination of solid phase and solution synthesis (hybrid approach). The synthesis of the peptide chain can be performed sequentially or by coupling of two or more short fragments to form a final sequence of a Bivalirudin molecule." *Id.* ¶ 11.

"In a particularly preferred embodiment of the present inventions, the suitably protected [B]ivalirudin peptide sequence contain[s] α-amino residues protected by Fmoc [9-fluorenylmethoxycarbonyl] while other functional residues of the amino acids are protected with suitable acid stable protecting groups." *Id.* ¶ 13.

The Specification describes one embodiment that involves preparing two subsequences of the Bivalirudin peptide, "fragment A" and "fragment B," which are ultimately coupled to yield Bivalirudin. *See id.* ¶¶ 14, 40, 79–85 (Examples 2–5). The Specification also discloses that Bivalirudin may be prepared "by known methods of elongating a peptide chain on a solid resin[, p]referably . . . by a stepwise Fmoc SPPS (solid phase peptide synthesis) procedure . . . ." *Id.* ¶ 43; *see also id.* ¶ 76 (Example 1 disclosing sequential stepwise addition of Fmoc-protected single amino acids to resin to yield Bivalirudin).

Claim 50, the sole independent claim, is representative and reads as follows (App. Br. 16):

50. A method of preparing Bivalirudin, comprising:

(a) preparing a Bivalirudin peptide sequence coupled to a resin via a linker molecule using solid phase synthesis,

wherein the preparation of the Bivalirudin peptide sequence comprises addition of single amino acids or combinations of amino acids to the resin to form a lengthening amino acid sequence,

wherein one or more of the amino acids being added to the lengthening amino acid sequence has a Fmoc (fluorenylmethyloxycarbonyl) protecting group on the α-amine,

wherein one or more of the amino acids being added to the lengthening amino acid sequence contains a protected side chain in addition to the Fmoc protected α-amine,

wherein a first intermediate sequence comprising Asp(X)^{11}-Phe^{12}-Glu(X)^{13}-Glu(X)^{14}-Ile^{15}-Pro^{16}-Glu(X)^{17}-Glu(X)^{18}-Tyr(X)^{19}-Leu^{20} (SEQ ID NO:11) is generated during the preparing, wherein X is a protecting group,

wherein a second intermediate sequence of Boc-D-Phe^{1}-Pro^{2}-Arg(X)^{3}-Pro^{4}-Gly^{5}-Gly^{6}-Gly^{7}-Gly^{8}-Asn(X)^{9}-Gly^{10}-Asp(X)^{11}-Phe^{12}-Glu(X)^{13}-Glu(X)^{14}-Ile^{15}-Pro^{16}-Glu(X)^{17}-Glu(X)^{18}-Tyr(X)^{19}-Leu^{20}-resin is generated during the preparing, wherein X is a protecting group, and

wherein Gly^{5}-Gly^{6} and Gly^{7}-Gly^{8} of Bivalirudin are added as di-mers or wherein Gly^{5}-Gly^{6}-Gly^{7}-Gly^{8} is added as a tetra-mer;

(b) treating the Bivalirudin peptide sequence coupled to the resin with a cleavage solution comprising an acid to remove the Bivalirudin peptide sequence from the resin and obtain crude Bivalirudin;

(c) recovering the crude Bivalirudin; and

> (d) purifying the crude Bivalirudin, wherein purified Bivalirudin does not contain more than 0.5% Asp^{9}-Bivalirudin as measured by high-performance liquid chromatography (HPLC).

The following rejections are before us for review:

(1) Claims 50, 51, 60, 61, 64–69, and 84–88, under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement (Ans. 2–4); and

(2) Claims 50, 51, 60, 61, 64–69, and 84–88, under 35 U.S.C. § 103(a), for obviousness over Angiomax,[2] Bruckdorfer,[3] Wellings,[4] Albericio II,[5] AB Technical Bulletin,[6] Okayama,[7] and Maraganore[8] (Ans. 5–11).

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[2] 2000 ANGIOMAX™ (Bivalirudin) Injection Information Sheets 1–11 (submitted with Information Disclosure Statement entered April 2, 2014).

[3] Thomas Bruckdorfer et al., *From Production of Peptides in Milligram Amounts for Research to Multi-Tons Quantities for Drugs of the Future*, 5 Current Pharmaceutical Biotechnology 29–43 (2004).

[4] Donald A. Wellings & Eric Atherton, *Standard Fmoc Protocols*, 289 Methods Enzymol. 44–67 (1997).

[5] Fernando Albericio, *Developments in peptide and amide synthesis*, 8 Current Opinion in Chemical Biology 211–21 (2004).

[6] Applied Biosystems Technical Bulletin: Cleavage, Deprotection, and Isolation of Peptides after Fmoc Synthesis 1–12 (1998).

[7] Toru Okayama et al., *Anticoagulant Peptides; Synthesis, Stability and Antithrombin Activity of Hirudin C-Terminal-Related Peptides and Their Disulfated Analog*, 44 Chem. Pharm. Bull. 1344–50 (1996).

[8] US 5,196,404 (issued Mar. 23, 1993).

WRITTEN DESCRIPTION

The Examiner's Position

The Examiner found that the recitation in claim 50, "wherein Gly^5-Gly^6 and Gly^7-Gly^8 of Bivalirudin are added as di-mers or wherein Gly^5-Gly^6-Gly^7-Gly^8 is added as a tetra-mer" (App. Br. 16), lacks adequate descriptive support in the original disclosure. Ans. 2–4.

In particular, the Examiner noted ¶¶ 11 and 43 of the Specification, but found that the disclosures therein did not describe, with sufficient specificity, adding the specific dimers and tetrameter recited in claim 50 to the Bivalirudin peptide being synthesized. *Id.* at 3–4. The Examiner also noted the Specification's disclosures regarding coupling fragments A and B, but again found those disclosures lacking sufficient specificity as to the particular dimers and tetramer recited in claim 50. *Id.*

Analysis

As stated in *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992):

> [T]he examiner bears the initial burden . . . of presenting a *prima facie* case of unpatentability. . . .
>
> After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument.

Appellants do not persuade us that a preponderance of the evidence fails to support the Examiner's finding that the recitation at issue in claim 50 lacks descriptive support in Appellants' Specification.

We agree with Appellants (*see* Reply Br. 2) that, "[i]n order to satisfy the written description requirement, the disclosure as originally filed does not have to provide *in haec verba* support for the claimed subject matter at

issue." *Purdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000).

Nonetheless, the original disclosure must convey with reasonable clarity to those skilled in the art that the inventor was in possession of the invention *as claimed*. *See id.* "Put another way, one skilled in the art, reading the original disclosure, must immediately discern the limitation at issue in the claims." *Id.*

For example, where an applicant had, by amendment, inserted into an application a claim to a specific chemical compound encompassed by the specification's generic disclosure, our reviewing court's predecessor found that the specification failed to describe the compound as being part of the invention because the specification lacked sufficient "blaze marks" to guide a skilled practitioner to the claimed compound from the broader disclosure. *In re Ruschig*, 379 F.2d 990, 995 (CCPA 1967).

As explained in *Ruschig*, "[s]pecific claims to single compounds require reasonably specific supporting disclosure and while we agree with the appellants . . . that naming is not essential, something more than the disclosure of a class of 1000, or 100, or even 48, compounds is required." *Id.*; *see also, Purdue Pharma v. Faulding*, 230 F.3d at 1326–27:

> As *Ruschig* makes clear, one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say here is my invention. In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure.

In the present case, the recitation at issue in claim 50 requires the use of one of two specific chemical compounds as intermediates in the claimed

synthetic process: (1) a Gly-Gly dimer or (2) a Gly-Gly-Gly-Gly tetramer. *See* App. Br. 16 (claim 50).

Appellants contend that, although ¶ 43 of the Specification describes a preferred synthetic embodiment that uses stepwise sequential addition of individual amino acids to generate the Bivalirudin peptide, ¶ 11 of the Specification provides adequate descriptive support for the dimeric and tetrameric intermediates recited in claim 50. App. Br. 6–7; Reply Br. 2.

We are not persuaded. The allegedly supporting disclosure states that the "synthesis of the peptide chain can be performed . . . by coupling of two or more short fragments to form a final sequence of a Bivalirudin molecule." Spec. ¶ 11.

As is evident, the portion of the Specification relied on as support for the claimed intermediates does not mention either of the intermediates required by claim 50 specifically, nor does the allegedly supporting disclosure even more generally mention either dimers or tetramers as intermediates. Rather, the allegedly descriptive disclosure recites only using "two or more short fragments" in the synthetic process. Spec. ¶ 11. Thus, as in *Ruschig*, the Appellants' Specification at best provides a generic description that encompasses the claimed intermediates, with insufficient specific guidance, or blaze marks, directing a skilled artisan to the particular intermediates required by the claims.

In that regard, Appellants contend that, because Bivalirudin consists of only 20 amino acids, "there is a small group of short fragments (e.g., dimers, tri-mers and tetra-mers) that could be immediately envisioned by one of ordinary skill in the art practicing the invention as claimed." App. Br. 7.

The recitation in ¶ 11 of "short fragments" of Bivalirudin, however, encompasses any dimer, trimer, tetramer, pentamer, hexamer, heptamer, octamer, and even larger subsequences, such as 10-, 11-, and 12-mers, of Bivalirudin. Given the broad scope of the short fragments encompassed by the disclosure of ¶ 11, and given Appellants' failure to advance any specific analysis or explanation as to the actual total number of species in the allegedly "small group" of fragments encompassed by the generic disclosure of ¶ 11, Appellants do not persuade us that the evidence of record supports their assertion that the set of intermediates described in ¶ 11 "is a small group . . . that could be immediately envisioned." App. Br. 7.

As explained in *Ruschig*, moreover, even a generic disclosure covering as few as 48 species is insufficient to provide descriptive support for an individual species encompassed by the genus, in the absence of specific guidance or blaze marks leading a skilled artisan to the particular claimed species at issue. *See Ruschig*, 379 F.2d at 995. In that regard, as noted above, the disclosure at issue in ¶ 11 of the Specification does not mention specifically either of the intermediates recited in claim 50, nor does the allegedly supporting disclosure mention specifically either dimers or tetramers as intermediates.

In sum, for the reasons discussed, Appellants do not persuade us that a preponderance of the evidence fails to support the Examiner's rejection of claims 50, 51, 60, 61, 64–69, and 84–88 for failure to comply with the written description requirement. We, therefore, affirm that rejection.

OBVIOUSNESS

The Examiner's Position

The Examiner's rejection, essentially, is that because Bivalirudin was a known therapeutic peptide having a known amino acid sequence, and because the Fmoc-based sequential addition of individual amino acids to a resin support was known to be an advantageous synthetic method for the production of therapeutic peptides, an ordinary artisan would have considered it obvious to prepare Bivalirudin using an Fmoc-based synthesis. *See* Ans. 8–15.

The Examiner summarized the rationale underlying the conclusion of obviousness as follows:

> Since Angiomax discloses that the synthetic bivalirudin is a trifluoroacetate salt, and it was known in the art that it was favorable to manufacture peptide drugs by using Fmoc chemistry in combination with a hyper acid labile resin and that trifluoroacetic acid produces trifluoroacetate salt (Bruckdorfer et al., Wellings et al., Albericio II), one of ordinary skill would have been motivated to prepare the synthetic bivalirudin trifluoroacetate salt in Angiomax by a Fmoc SPPS approach comprising the steps of preparing a bivalirudin amino acid sequence coupled to a hyper acid labile resin (i.e. CTC resin) using Fmoc SPPS, wherein the preparation comprises anchoring a first protected amino acid to the hyper acid labile resin and adding more protected amino acids to synthesize the bivalirudin peptide; cleaving the synthesized bivalirudin peptide from the resin; recovering the crude bivalirudin peptide; and purifying the crude bivalirudin peptide by HPLC.

Ans. 8–9. The Examiner further reasoned that the purity of the final product would have been obvious, "since it was known that [F]moc chemistry can produce peptides > 95% purity (at least Wellings et al. p. 60) and that

additional purification by HPLC can be used to further increase the purity (Bruckdorfer et al. p. 33)." *Id.* at 8–9.

Analysis

Appellants do not argue any of the claims subject to this ground of rejection separately. *See* App. Br. 6–15; Reply Br. 2–4. We select claim 50 as representative of the rejected claims. *See* 37 C.F.R. § 41.37(c)(1)(iv).

Appellants do not persuade us that a preponderance of the evidence fails to support the Examiner's prima facie case of obviousness. To the contrary, we agree with the Examiner's findings of fact and conclusion that claim 50 would have been obvious to an ordinary artisan, and adopt those findings and conclusion as our own. We address Appellants' arguments below.

Appellants contend initially that, although "the amino acid sequence of bivalirudin was known at the time of the invention, along with SPPS [(solid phase peptide synthesis technology)], what was not known was the specific sequence of steps and the reagents that would be required to produce bivalirudin using SPPS." App. Br. 13; *see also* Reply Br. 3. In particular, Appellants contend, given the inherent challenges presented by SPPS, the combination of references cited by the Examiner "does not teach or suggest, for example, the ten amino acid intermediate recited in claim 50 (lines 13-15) where the asparagine residue at position 11 is protected, where the phenylalanine at position 12 is not protected, where the glutamic acid at position 13 is protected, etc." App. Br. 13–14.

We are not persuaded. Example 4 of Maraganore discloses a process of making Bivalirudin (there termed Hirulog-8) that includes each of the basic steps required by Appellants' claim 50—solid phase peptide synthesis

on a resin substrate (step (a) of claim 50), cleavage from the resin (step (b)), recovery of the crude peptide (step (c)), and recovery of the pure peptide (step (d)). Maraganore 19:49–20:29.

Maraganore describes its solid phase synthesis as being performed by stepwise addition of the amino acids constituting the Bivalirudin peptide to a resin substrate, as required by claim 50, and, as the claim requires, discloses that "[i]n order to achieve higher yields in synthesis, the $(Gly)_4$ linker segment was attached in two cycles of manual addition of BOC[t-Butyloxycarbonyl]-glycylglycine." *Id.* at 19:64–67; *see also* App. Br. 16 (claim 50 reciting "wherein Gly^5-Gly^6 and Gly^7-Gly^8 of Bivalirudin are added as di-mers or wherein Gly^5-Gly^6-Gly^7-Gly^8 is added as a tetra-mer"). As the Examiner points out, addition of the amino acids to the resin in the order taught in Maraganore results in the intermediates having the same amino acid sequence of the two intermediates recited in claim 50.

Although Maraganore, thus, differs from claim 50 in that it uses a Boc protecting group on the α-amine rather than the Fmoc group required by claim 50, as noted in several references cited by the Examiner, Fmoc-based solid phase synthesis was known in the prior art, and had supplanted Boc-based synthesis for a number of reasons, including improved ease of use and less harsh conditions. *See, e.g.*, Bruckdorfer 32 (Fmoc-based synthesis "avoids the use of final harsh conditions required in the Boc/Bzl strategy. SPPS is very common today for small scale synthesis because almost every peptide sequence can be built with standard reaction procedures . . ."); Wellings 45 (describing Fmoc-based synthesis as "operationally simple and chemically less complex than the Boc procedure," as "a mild procedure,"

and as "the method of choice for the solid-phase synthesis of most modified peptide species").

As to the differences in protected amino acids between Maraganore and the intermediates recited in claim 50, as the Examiner pointed out, the AB Technical Bulletin discloses that, when performing Fmoc-based synthesis, the side chains of arginine, asparagine, aspartic acid, glutamic acid, and tyrosine require protecting groups, whereas phenylalanine, proline, glycine, isoleucine, and leucine do not. *See* AB Technical Bulletin, Table 1. That is, the AB Technical Bulletin makes it clear that, when performing Fmoc-based peptide synthesis, protecting groups are required on the side chains of the same amino acids having protecting groups in Appellants' claim 50, and no protecting group is required for the amino acids that are unprotected in claim 50.

Thus, given the desirability in the art of using Fmoc-based synthesis, and given that using that technique requires protection of the side chains of the same amino acids protected in the two intermediates in Appellants' claim 50, Appellants do not persuade us that the cited references fail to suggest the specific intermediates recited in claim 50.

Appellants contend that an ordinary artisan would not have recognized that adding Gly^5-Gly^6 and Gly^7-Gly^8 of Bivalirudin as a dimer or adding Gly^5-Gly^6-Gly^7-Gly^8 as a tetramer, as recited in claim 50, would have alleviated the problem of adding too many or too few glycines to the peptide, encountered by Appellants when developing the synthetic method.

App. Br. 14–15 (citing the Far Declaration).[9] Appellants contend, moreover, that an ordinary artisan synthesizing Bivalirudin by Fmoc-based methods would not have attached the $(Gly)_4$ segment (i.e., Gly^5-Gly^6-Gly^7-Gly^8) in two cycles of addition of glycylglycine (Gly-Gly) as taught by Maraganore because of the differences in chemistry between Maraganore's Boc-based synthesis, and Fmoc synthesis. App. Br. 15; *see also* Reply Br. 4.

We are not persuaded. As noted above, Maraganore discloses that "[i]n order to achieve higher yields in synthesis, the $(Gly)_4$ linker segment was attached in two cycles of manual addition of BOC-glycylglycine." Maraganore 19:64–67.

Given this teaching, we agree with the Examiner that an ordinary artisan performing Fmoc-based synthesis of Bivalirudin would have been motivated to synthesize the peptide's Gly^5-Gly^6-Gly^7-Gly^8 segment in the same way as taught in Maraganore. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007) ("[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill").

Moreover, even assuming that Appellants' purpose for using dimers or a tetramer (avoiding incorporation of excess or insufficient glycines) is different than the reason suggested by the art (yield improvement), that difference does not support a conclusion of nonobviousness. *See id.* at 419 ("In determining whether the subject matter of a patent claim is obvious,

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[9] Declaration of Adel Rafai Far under 37 C.F.R. § 1.132 (declaration executed March 16, 2015).

neither the particular motivation nor the avowed purpose of the patentee controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103").

Appellants, moreover, do not advance any specific persuasive evidence supporting their assertion that an ordinary artisan, based on the differences between Fmoc-based and Boc-based syntheses, would have expected that Maraganore's technique of synthesizing Bivalirudin's Gly^5-Gly^6-Gly^7-Gly^8 segment would not work in an Fmoc-based synthesis. As our reviewing court has explained, "[o]bviousness does not require absolute predictability of success. . ., all that is required is a reasonable expectation of success." *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988) (internal quotation and emphasis removed)).

In sum, for the reasons discussed, Appellants do not persuade us that a preponderance of the evidence fails to support the Examiner's conclusion that claim 50 would have been obvious to an ordinary artisan in view of the cited references. We, therefore, affirm the Examiner's rejection of claim 50 for obviousness. Because they were not argued separately, claims 51, 60, 61, 64–69, and 84–88 fall with claim 50. *See* 37 C.F.R. § 41.37(c)(1)(iv).

SUMMARY

For the reasons discussed, we affirm each of the Examiner's rejections.

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED